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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/080,919 | 02/22/2002 | Lucia Irene Gonzalez-Villasenor | 22918/1 | 7790 |

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| EXAMINER | |
|---|---|
| MONDESI, ROBERT B | |
| **ART UNIT** | **PAPER NUMBER** |
| 1653 | |

DATE MAILED: 11/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/080,919 | GONZALEZ-VILLASENOR, LUCIA IRENE | |
| | Examiner | Art Unit | |
| | Robert B Mondesi | 1653 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *03 November 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

### *Priority*

The current application filed on February 22, 2002 claims priority to an earlier provisional application 60/270,839 filed on February 23, 2001. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification of in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number.

### *Specification*

The disclosure is objected to because of the following informalities: The use of the trademarks Q-SEPHAROSE, SEPHAROSE, SEPHRACYL, (page 48, line 9) MANTON GAVLIN and MICROFLUIDIZER (page 34, line 18) have been noted in this application. They should be capitalized (entire word) wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Applicant is reminded of the proper language and format for an abstract of the disclosure. The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "wherein" (line 10) should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.
Appropriate corrections are required.

***Information Disclosure Statement***

The IDS filed February 22, 2002 has been received and is signed and considered, a copy of the IDS is attached to the following document.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

**Claims 1-16, 20, 26-43 and 46** are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

**In claims 1, 26, 42 and 43** it is not clear what is meant by "recovering". The applicant explains (in the specification on page 14, lines 19-22) that, "recovering shall mean that the protein is recovered from inclusion bodies in a non-denatured form but altered tertiary structure". The term "recovering" is clear in reference to insoluble target

peptides (page 63, line 3-5) but as far as referring to; the "recovery of the lysate" (page 63, line7, page 66, line10), the "recovery of the supernatant" (page 63, line 15) and the "recovery of precipitate-free supernatant" (page 68, line 18 and page 69, line 11) the applicant has not clarified the definition of recovering. None of the dependent **claims 2-16, 27-41** clarify further the term "recovery".

In **claim 2** the phrase "substantially free" is indefinite. The applicant has failed to define to what degree the solubilization solution is free of detergent. The use of the word substantial results in an undefined range of possible variants. Also the word "detergent" has not been defined by the applicant. A detergent can be a variety of compounds or compositions of compounds- depending on the intended use.

The term " between about" in **claims 1, 4, 5, 6, 8, 22, 24-26, 29-32, 34, 42-44 and 46-48** is a relative term which renders the claims indefinite. The term "between about" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is unclear as what is considered to be the range of "between about" in the above claims. For instance in claim 1, is the concentration of sodium hydroxide limited to between 8 mM to 10 mM or about 8 mM and 10 mM. If the claim is limited to about, to what extent is the concentattion of sodium hydroxide below 8 mM and above 10 mM.

"Protein" in **claim 17**, per se, has no antecedent basis in claim 1which only indicates "peptide" and "Polypeptide".

**Claims 17-18** are directed to products and should be written in independent format from method **claims 1-16**.

In **claim 20** the phrase "formulating target peptide" is unclear. Formulating has different meanings, each of which can be associated with an independently different method steps, for example formulating pharmaceutical compositions involves different steps than the method steps presented by the applicant in **claim 20**. **Claims 21-25** do not further clarify "formulating".

In **claim 26** the words "bioactive" and "the" are juxtaposed. The correct order is "the bioactive" not "bioactive the".

**Claim 26** recites the limitation "solubilization preparation of (c) " in lines 17-18. There is insufficient antecedent basis for this limitation in the claim.

In **claim 28,** the limitation "detergent" has not been defined by the applicant in the specification. A detergent can be a variety of compounds or compositions of compounds- depending on the intended use. In the instant case the ordinary and accepted meaning, "cleansing or purging agent", (Stedman's Medical Dictionary, page 198, column 1) of detergent will be applied.

In **claim 34** the identifier "a" is missing before the word "concentration".

In **claims 42 and 43** the phrase "at least about" is indefinite because it allows for an undefined range. Also the phrase "10% more pure" is indefinite because the applicant has not defined how purity is determined.

In **claim 46** the word "abot" is misspelled. The correct spelling is "about".

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

**Claims 17-19** are rejected under 35 U.S.C. 102(b) as being anticipated by Moses et al. (cited in IDS filed June 1, 2003). **Claims 18-19** disclose that Troponin I, a protein from the Troponin family is produced by the method presented in **claim 1**. These claims are in product by process format absent factual evidence to the contrary, the product is not different fro the prior since the process steps do not contain indicia of production of a product with new physical, chemical and biological properties and functions. Moses et al. teach, the production and purification of non-recombinant and recombinant protein, Troponin I in the Materials and methods of their publication (pages 2645-2646) (**present claims 17-19**). Thus Moses et al. teach all the elements of claims 17-19 and these claims are anticipated under 35 USC 102(b).

**Claims 20-21** rejected under 35 U.S.C. 102(b) as being anticipated by Lee et al. Lee et al. disclose the product Troponin ; and a method comprising dialyzing and ultrafiltering a polypeptide into an aqueous buffer that is denaturant free wherein the polypeptide is Troponin (column 10 lines 32-39). Lee et al. also teach that the dialized samples containing Troponin are dispensed into vials or tubes (column 10, lines 38-40)

(**Present claims 20-21**). Thus Lee et al. teach all the elements of claims 17-19 and these claims are anticipated under 35 USC 102(b).

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

**Claims 1-6,15 and 43** are rejected under 35 U.S.C. 103(a) as being unpatentable over Mahmoud et al. (cited in IDS filed June 1, 2003) in view of Dorin et al. United States Patent 4,748,234. Mahmoud et al. teach a solubilization and purification method wherein an insoluble target peptide was purified from a host organism. The above method includes disrupting the host cell (page 658, section 2.4, line 9) to produce a lysate and dissolving the precipitate containing the target peptide in a solubilization solution comprising sodium hydroxide a concentration of about 9.5 mM at a pH of 10.5 (section 2.5, page 659, lines 16-24). Mahmoud et al. also teach that the solubilized protein is present in the host cell inclusion bodies (section 2.5, page 659, lines 16-24) and is purified (section 2.5 page 659, lines 30-45). Mahmoud et al. do not teach a protein concentration of about 1mg and 4 mg per ml in the solubilization solution. Dorin et al. teach a polypeptide concentration of about 1mg and 4mg per ml (table VII). One of ordinary skill in the art would have combined the Mahmoud et al. and Dorin et al. for

the advantages of a method of solubilizing and recovering a target peptide from a host organism involving; disrupting the host cell, resuspending the lysate in a solubilization solution comprising a sodium hydroxide concentration of about 8 mM and 10 mM, a polypeptide concentration of about 1mg and about 4mg with a pH of about 9 and about 11.2 and purifying the target plypeptide present in the host inclusion bodies (**present claims 1-6, 15 and 43**). As combined, Mahmoud et al. and Dorin et al. demonstrate that one of ordinary skill in the art would have made and used the claimed invention prior to the time the claimed invention was made. Thus the claimed invention was prima facie- obvious at the time it was made.

**Claims 7-13** are rejected under 35 U.S.C. 103(a) as being unpatentable over Mahmoud et al. as applied to **claim 1** above, and further in view of Dorin et al. United States Patent 4,748,234 and Schein (cited in IDS filed June 1, 2003). **Claims 7-11** are further limitations of **claim 1** citing the use of stabilizing compounds such as sugar, polyol, or amino acids amino acid. Mahmoud et al do not teach the addition of such stabilizing agents to the solubilization solution. Schein discloses that stabilizing sugar, amino acid and stabilizing polyol can be can be included with solubilization solutions (page 313, Table 1) (**present claims 7, 9, and 10**). Schein further teaches that the concentration of stabilizing compound is about 20 mM (page 313, Table 1) (**present claim 8**). Schein does not teach the limitation of **claim 11** that the stabilizing sugar is lactose. Dorin et al disclose that stabilizing sugars can be disaccharides (column 6, line 53) (**present claim 11**). **Claims 12 and 13** are further limitations of **claim 7**. Mahmoud et al. and Schein do not disclose that the host organism is E. Coli. Dorin et al. teach that

the host organism used for the production of target protein is E. Coli (**present claims 12 and 13).** One of ordinary skill in the art would have combined Mahmoud et al., Dorin et al. and Schein et al. for the advantages of a solubilization solution containing stabilizing compounds such as lactose, amino acids and polyol at a concentration of about 20 mM , used in a method of target protein recovery and purification wherein the host cell is E.Coli. As combined, Mahmoud et al., Dorin et al. and Schein demonstrate that one of ordinary skill in the art would have made and used the claimed invention prior to the time the claimed invention was made. Thus the claimed invention was prima facie-obvious at the time it was made.

**Claim 16** is rejected under 35 U.S.C. 103(a) as being unpatentable over Mahmoud et al. as applied to **claim 1** above, and further in view of Dorin et al. United States Patent 4,748,234 and Liu et al. United States Patent 5,834,210. Mahmoud et al. and Dorin et al. do not teach a solublization and recovery method wherein the target protein is troponin or a subunit of troponin. Liu et al. disclose a solubilization and recovery method wherein the target peptide is troponin (examples 1, 2 and 3). One of ordinary skill in the art would have combined Mahmoud et al, Dorin et al. and Liu et al. for the advantages of a method of solubilizing and recovering a target peptide from a host organism. This method involving; disrupting the host cell, resuspending the lysate in a solubilization solution comprising; a sodium hydroxide concentration of about 8 mM and 10 mM, a polypeptide concentration of about 1mg and about 4mg and a pH of about 9 and about 11.2. Also further purifying the target polypeptide wherein the target peptide is troponin or a subunit of toponin (**present claim 16**). As combined, Mahmoud

et al. Dorin et al. and Liu et al. demonstrate that one of ordinary skill in the art would have made and used the claimed invention prior to the time the claimed invention was made. Thus the claimed invention was prima facie- obvious at the time it was made.

**Claims 26-32, 38-39, and 41-42** are rejected under 35 U.S.C. 103(a) as being unpatentable over Dorin et al. United States Patent 4,748,234 in view of Darling et al. United States Patent 5,530,100, Couche et al and Schein. Dorin et al. teach a solubilization and purification method wherein an insoluble target peptide was purified from a host organism. The above method includes disrupting the host cell to produce a lysate and dissolving the precipitate containing the target peptide in a solubilization solution (example 1,2 and 3) wherein the polypeptide concentration is about 1mg and about 4mg per ml (table VII). Dorin et al. also teach that the solubilized protein is present in the host bacterial cell, E. Coli, inclusion bodies (example 1, 2 and 3). Dorin et al. do not teach that the concentration of HCL in the solubilization solution is about 10 and about 20 mM or that the pH of the solubilization solution is between about 2.0 an about 3.0. Darling et al, teach that the concentration of HCl in the solubilization preparation is about 10 and 20 mM (example II). Dorin et al and Darling et al. do not teach that the pH of the solubilization preparation is between about 2.0 and about 3.0 or is adjusted to 9.5 with NaOH. Couche et al. teach that the pH of the solubilization is about 2.0 and 3.0 and can be adjusted to 9.5 with NaOH (table 1, 5284). One of ordinary skill in the art would have combined Dorin et al., Darling et al. and Couche et al for the advantages of a method of solubilizing and recovering a target peptide from a host organism involving; disrupting the host cell, resuspending the lysate in a

solubilization solution comprising a hydrogen chloride concentration of about 10 mM and 20 mM, a polypeptide concentration of about 1mg and about 4mg with a pH of about 2 and about 3, adjusting the pH to 9.5 with NaOH and purifying the target polypeptide present in the host bacterial cell, E. Coli, inclusion bodies (**present claims 26-32, 38-39, and 41-42**). As combined, Dorin et al., Darling et al. and Couch et al. demonstrate that one of ordinary skill in the art would have made and used the claimed invention prior to the time the claimed invention was made. Thus the claimed invention was prima facie- obvious at the time it was made.

**Claims 33-37** are rejected under 35 U.S.C. 103(a) as being unpatentable over Dorin et al. as applied to **claim 26** above, and further in view of Darling et al. United States Patent 4,530,100 Couche et al and Schein. **Claims 33-37** are further limitations of **claim 26** citing the use of stabilizing compounds such as sugar, polyol, or amino acids amino acid. Dorin et al. Darling et al. and Couche et al. do not teach the addition of such stabilizing agents to the solubilization solution. Schein discloses that stabilizing sugar, amino acid and stabilizing polyol can be can be included with solubilization solutions (page 313, Table 1) (**present claims 33, 355-36** ). Schein further teaches that the concentration of stabilizing compound is about 20 mM (page 313, Table 1) (**present claim 36**). Schein does not teach the limitation of **claim 37** that the stabilizing sugar is lactose. Dorin et al disclose that stabilizing sugars can be disaccharides or polysaccharides (column 6, line 53) (**present claim 37**). One of ordinary skill in the art would have combined Darling et al., Dorin et al., Couche et al. and Schein et al. for the advantages of a solubilization solution containing stabilizing compounds such as lactose

, amino acids and polyol at a concentration of about 20 mM , used in a method of target protein recovery and purification involving; disrupting the host cell, resuspending the lysate in a solubilization solution comprising a hydrogen chloride concentration of about 10 mM and 20 mM, a polypeptide concentration of about 1mg and about 4mg with a pH of about 2 and about 3. As combined, Darling et al., Dorin et al., Couche et al., Schein et al. demonstrate that one of ordinary skill in the art would have made and used the claimed invention prior to the time the claimed invention was made. Thus the claimed invention was prima facie- obvious at the time it was made.

**Claims 44- 47** are rejected under 35 U.S.C. 103(a) as being unpatentable over Olson et al. United States Patent 4,511,503 in view of Schein et al. Olson et al. teach a method for preparing bioactive recombinant polypeptides in a chaptrope containing solution, comprising: decreasing the concentration of chatropic containing solution against a renaturing buffer of pH between about 9 and between about 11.2 (column 19 lies 10-70) and buffer concentration between about 10 and about 50 mm (examples 1-9). Olson et al. further disclose that recombinant protein is chromatographically purified. Oslon et al do not teach that the renaturing buffer further comprises a stabilizing compound wherein the stabilizing compound is a sugar at about 2 and 12 mM oe polyol at about 5 and 500 mM. Schein discloses a renaturing buffer comprising a stabilizing compound wherein the stabilizing compound is a sugar at about 2 and 12 mM or polyol at about 5 and 500 mM (table 1, page 313). One of ordinary skill in the art would have combined Olson et al. and Schein for the advantages of a method for preparing bioactive recombinant polypeptides in a chaptrope containing solution, comprising:

decreasing the concentration of chatropic containing solution against a renaturing buffer of pH between about 9 and between about 11.2 and buffer concentration between about 10 and about 50 mm wherein the buffer further comprises a stabilizing compound that is a sugar at about 2 and 12 mM or polyol at about 5 and 500 mM (present claims 44-47). As combined, Olson et al, Schein demonstrate that one of ordinary skill in the art would have made and used the claimed invention prior to the time the claimed invention was made. Thus the claimed invention was prima facie- obvious at the time it was made.

***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert B Mondesi whose telephone number is 703-305-4445. The examiner can normally be reached on 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 703-308-2923. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0198.

Christopher S. F. Low

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